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Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

PURINE DERIVATIVES

2 Applicant's details

☑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

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Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH
KENT

6892673001

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
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2d, 2e and 2f:
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Second applicant (if any)

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3
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3a Have you appointed an agent to deal with your application?

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⬇
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Agent's name
K. S. RUDDOCK
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

6296446001

Agent's ADP number

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

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4 Agent's or applicant's reference number *(if applicable)* PCS10334KSR-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ ***go to 6***

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❑ number of earlier application or patent number

❑ filing date

(day month year)

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 Declaration of priority

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- any applicant is not an inventor
- there is an inventor who is not an applicant, or
- any applicant is a corporate body.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)		Description	18
Abstract		Drawing(s)	

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

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I/We request the grant of a patent on the basis of this application.

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PURINE DERIVATIVES

This invention relates to purine derivatives. More particularly, this invention relates to 9-(tetrahydro-2-furanyl)-9H-purine-2-carboxamide derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

These derivatives are selective, functional agonists of the human adenosine A2a receptor and may be used as anti-inflammatory agents in the treatment of, *inter alia,* diseases of the respiratory tract.

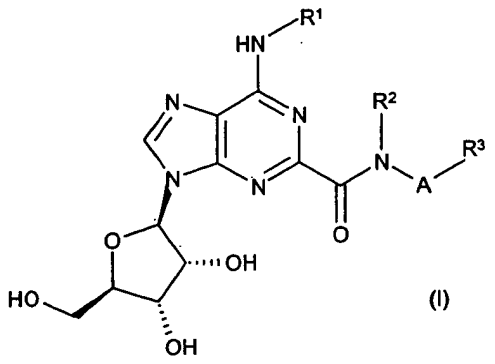
Adenosine is a ubiquitous molecule having a central role in mammalian intermediary metabolism. Independently, adenosine acts on multiple surface receptors to produce a variety of responses. Adenosine receptor classification has revealed the presence of at least four subtypes: A1, A2a, A2b and A3. Stimulation of adenosine A2 receptors on the surface of human neutrophils has been reported to potently inhibit a range of neutrophil functions. Activated neutrophils can damage lung tissue by release of reactive oxygen species, for example, superoxide anion radicals ($O_2^{\cdot-}$), and granule products, for example, human neutrophil elastase (HNE), amongst other inflammatory mediators. In addition, activated neutrophils perform both *de novo* synthesis and release of arachidonate products such as leukotriene B_4 (LTB_4). LTB_4 is a potent chemo-attractant that recruits additional neutrophils to the inflammatory focus, whereas released $O_2^{\cdot-}$ and HNE adversely affect pulmonary extracellular matrix. The A2 receptor subtype mediating many of these responses ($O_2^{\cdot-}$ and LTB_4/HNE release and cell adhesion) is established as A2a. The A2 subtype (A2a or A2b) mediating the other effects remains to be established.

Selective agonist activity at the A2a receptor is considered to offer greater therapeutic benefit than the use of non-selective adenosine receptor agonists because interaction with other subtypes is associated with detrimental effects in the lung in animal models and human tissue studies. For example, asthmatics, but not non-asthmatics, bronchoconstrict when challenged with inhaled adenosine. This response is at least in part due to the activation of the

A1 receptor subtype. Activation of A1 receptors also promotes neutrophil chemotaxis and adherence to endothelial cells, thus promoting lung injury. Furthermore, many patients with respiratory disease will be co-prescribed β_2-agonists, and negative interaction has been shown in animal studies between isoprenaline and adenosine receptors negatively coupled to adenylate cyclase. Degranulation of human mast cells is promoted by activation of adenosine A2b receptors, thus selectivity over the A2b receptor is also advantageous.

The present purine derivatives are selective A2a receptor agonists that can inhibit neutrophil function. They can be used as anti-inflammatory agents in the treatment of diseases of the respiratory tract, for example, adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema and rhinitis. They are also effective in the treatment of septic shock, male erectile dysfunction, hypertension, stroke, cerebral ischemia, peripheral vascular disease, wound healing and psychotic disorders.

Accordingly, the present invention provides a compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof,

wherein R^1 is hydrogen or C_1-C_6 alkyl substituted by 1 or 2 substituents each independently selected from phenyl and naphthyl;

R^2 is hydrogen or C_1-C_6 alkyl;

A is C_1-C_6 alkylene; and

R^3 is phenyl, naphthyl, C_3-C_8 cycloalkyl, azetidinyl, pyrrolidinyl, piperidinyl, amino, -NH(C_1-C_6 alkyl) or -N(C_1-C_6 alkyl)$_2$, said phenyl, naphthyl, C_3-C_8 cycloalkyl, azetidinyl, pyrrolidinyl and piperidinyl being optionally substituted by one or more substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo(C_1-C_6)alkyl, halo and cyano:

with the proviso that when R^3 is N-linked, optionally substituted-azetidinyl, -pyrrolidinyl or -piperidinyl, or is amino, -NH(C_1-C_6 alkyl) or -N(C_1-C_6 alkyl)$_2$, A is C_2-C_6 alkyl.

In the above definitions, halo means fluoro, chloro, bromo or iodo and alkyl and alkylene groups containing the requisite number of carbon atoms can be unbranched- or branched-chain.

The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc and diethanolamine salts.

For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19, 1977.

The pharmaceutically acceptable solvates of the compounds of the formula (I) include the hydrates thereof.

Also included within the present scope of the compounds of the formula (I) are polymorphs thereof.

A compound of the formula (I) may contain one or more additional asymmetric carbon atoms and therefore exist in two or more stereoisomeric

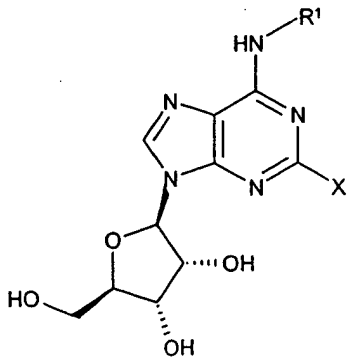
forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) together with mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

A particularly preferred example of a compound of the formula (I) is 9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide (as described in the Example section hereafter), together with pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can be prepared using conventional procedures such as by the following illustrative method in which R^1, R^2, R^3 and A are as previously defined for a compound of the formula (I) unless otherwise stated.

All the compounds of the formula (I) can be prepared by reaction of a compound of the formula:



(II)

wherein X is bromo, iodo, -Sn(C_1-C_{12} alkyl)$_3$ or CF_3SO_2O-, preferably iodo, with a compound of the formula:

$$R^2NH\text{-}A\text{-}R^3$$

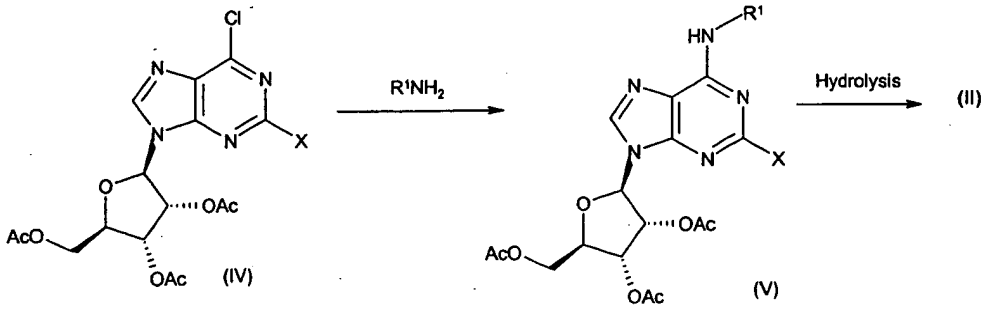
(III)

in the presence of carbon monoxide and a suitable coupling catalyst. Preferably, the catalyst is a palladium (II) catalyst, more preferably 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) 1:1 complex with dichloromethane.

In a typical procedure the reaction is carried out in a sealed vessel in the presence of carbon monoxide at a pressure of about 345kPa (50psi), at an elevated temperature, e.g. about 60°C, and in a suitable solvent, e.g. tetrahydrofuran.

The intermediates of the formula (II) can be prepared as shown in Scheme 1.

Scheme 1



wherein X is as previously defined for a compound of the formula (II) and "Ac" is acetyl.

In a typical procedure a compound of the formula (IV) is reacted with an amine of the formula R^1NH_2 in the presence of a suitable acid acceptor, e.g. triethylamine, and in a suitable solvent, e.g. acetonitrile, at an elevated temperature, as necessary. The product of the formula (V) obtained can be hydrolysed to a compound of the formula (II) by a conventional procedure such as by using a suitable base, e.g. sodium carbonate, and in a suitable solvent, e.g. aqueous methanol.

The intermediates of the formula (III) and (IV) are either known compounds or can be prepared by conventional procedures.

All of the above reactions and the preparations of novel starting materials using in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the Example and Preparations hereto.

A pharmaceutically acceptable salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The anti-inflammatory properties of the compounds of the formula (I) are demonstrated by their ability to inhibit neutrophil function which indicates A2a receptor agonist activity. This is evaluated by determining the compound profile in an assay where superoxide production was measured from neutrophils activated by fMLP. Neutrophils were isolated from human peripheral blood using dextran sedimentation followed by centrifugation through Ficoll-Hypaque solution. Any contaminating erythrocytes in the granulocyte pellet were removed by lysis with ice-cold distilled water. Superoxide production from the neutrophils was induced by fMLP in the presence of a priming concentration of

cytochalasin B. Adenosine deaminase was included in the assay to remove any endogenously produced adenosine that might suppress superoxide production. The effect of the compound on the fMLP-induced response was monitored colorometrically from the reduction of cytochrome C within the assay buffer. The potency of the compounds was assessed by the concentration giving 50% inhibition (IC_{50}) compared to the control response to fMLP.

The compounds of the formula (I) can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the formula (I) can be administered orally, buccally or sublingually in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, sustained-, pulsed- or controlled-release applications.

Such tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or a high molecular weight polyethylene glycol. For aqueous suspensions and/or elixirs, the compounds of the formula (I) may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol or glycerin, and combinations thereof.

The compounds of the formula (I) can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally,

intraventricularly, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) will usually be from 0.01 to 100 mg/kg, preferably from 0.1 to 100 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the formula (I) may contain from 5 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compounds of formula (I) can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and

cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the formula (I) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 20 to 4000 μg of a compound of the formula (I) for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 20μg to 20mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. The compounds of the formula (I) may also be transdermally administered, for example, by the use of a skin patch.

For application topically to the skin, the compounds of the formula (I) can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Thus the invention provides:-

(i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having A2a receptor agonist activity;

(vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of an anti-inflammatory agent;

(vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;

(viii) use as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema and rhinitis;

(ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, cerebral ischemia, peripheral vascular disease, wound healing or a psychotic disorder;

(x) a method of treatment of a mammal, including a human being, with a A2a receptor agonist including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema and rhinitis;

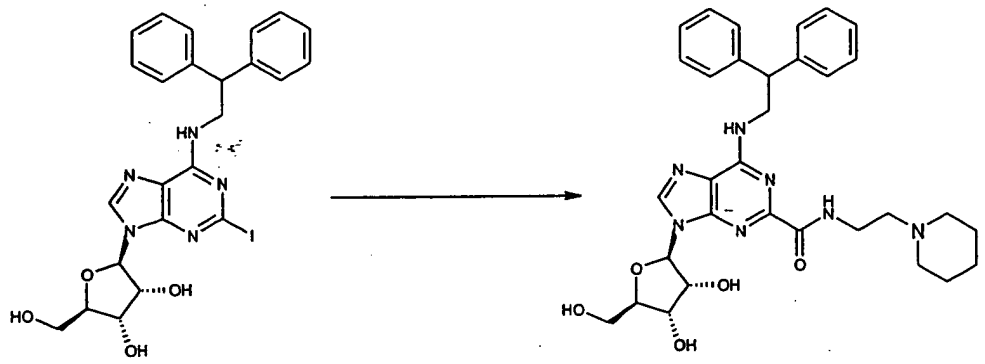
(xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, cerebral ischemia, peripheral vascular disease, wound healing or a psychotic disorder including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and

(xv) any novel intermediate disclosed herein.

The following Example illustrates the preparation of the compounds of the formula (I):-

EXAMPLE 1

9-[(2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)tetrahydro-2-furanyl]-6-[(2,2-diphenylethyl)amino]-*N*-[2-(1-piperidinyl)ethyl]-9*H*-purine-2-carboxamide



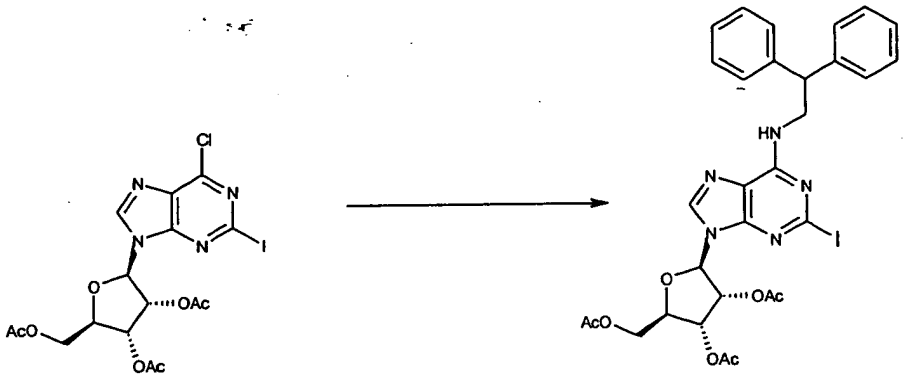
A solution of (2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-diphenylethyl)amino]-2-iodo-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol (5g, 8.7mmol) (see Preparation 2), 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) 1:1 complex with dichloromethane (0.7g, 0.9mmol) and 1-(2-aminoethyl)piperidine (3.4g, 26.5mmol) in anhydrous tetrahydrofuran (250ml) was heated at 60°C, under a carbon monoxide atmosphere at 345kPa (50psi) in a sealed vessel for 24 hours. The mixture was cooled, filtered through a pad of arbacel (trade mark) filter aid and the filtrate diluted with tetrahydrofuran (150ml) and ethyl acetate (400ml). The resulting solution was washed with water (3x300ml) and the organic phase extracted with 2N aqueous hydrochloric acid solution (50ml). The acidic aqueous phase was washed with ethyl acetate (20ml) then basified to pH >7 by addition of 0.88 aqueous ammonia solution. Ethyl acetate (100ml) was added and the mixture stirred for 10 minutes after which time a white solid formed. This solid was filtered, washed sequentially with water and ethyl acetate and dried at 70°C under reduced pressure to yield the title compound as a white solid (2.8g).

^{1}H-NMR ($CDCl_3$): δ = 8.49 (1H, s), 8.30 (1H, s), 7.20-7.35 (10H, m), 5.97 (1H, d), 5.85 (1H, br s), 4.70 (1h, br s), 4.60 (1H, t), 4.20-4.40 (3H, m), 3.96-4.08 (2H, q), 3.40-3.53 (2H, m), 2.50 (2H, t), 2.30-2.40 (4H, br s), 1.50-1.70 (3H, br s), 1.03-1.41 (3H, br m).

The following Preparations describe the preparation of certain intermediates used in the preceding Example.

PREPARATION 1

(2*R*,3*R*,4*R*,5R)-4-(Acetyloxy)-2-[(acetyloxy)methyl]-5-{6-[(2,2-diphenylethyl)amino]-2-iodo-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate



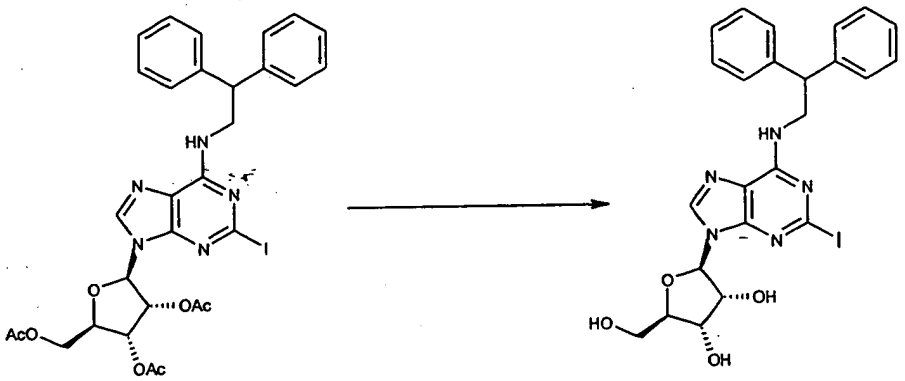
("Ac" is acetyl)

A mixture of (2*R*,3*R*,4*R*,5*R*)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-(6-chloro-2-iodo-9*H*-purin-9-yl)tetrahydro-3-furanyl acetate (J. Med. Chem., 35, 248, 1992) (15.2g, 28.2 mmol), 2,2-diphenylethylamine (6.1g, 30.9mmol) and triethylamine (11.4g, 112.8mmol) in acetonitrile (200ml) was stirred at room temperature, under a nitrogen atmosphere, for 24 hours, followed by heating under reflux for 90 minutes. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (500ml) and the solution washed with water (200ml). The organic phase was separated and the solvent removed under reduced pressure to give the title compound as a pale yellow foam (18.8g).

^{1}H-NMR ($CDCl_3$): δ = 7.70 (1H, s), 7.20-7.39 (10H, m), 6.11 (1H, d), 5.75 (2H, t), 5.61 (1H, m), 4.20-4.48 (6H, m), 2.19 (3H, s), 2.13 (3H, s), 2.09 (3H, s).

PREPARATION 2

(2*R*,3*R*,4*S*,5*R*)-2-{6-[(2,2-Diphenylethyl)amino]-2-iodo-9*H*-purin-9-yl}-5-(hydroxymethyl)tetrahydro-3,4-furandiol



(2*R*,3*R*,4*R*,5R)-4-(acetyloxy)-2-[(acetyloxy)methyl]-5-{6-[(2,2-diphenylethyl)amino]-2-iodo-9*H*-purin-9-yl}tetrahydro-3-furanyl acetate (1.7g, 2.43mmol) (see Preparation 1) was dissolved in a 10:1, by volume, mixture of methanol : water (88ml). Solid sodium carbonate (1.5g, 14.1mmol) was added and the mixture stirred at room temperature for 90 minutes before removing the methanol under reduced pressure. The residual aqueous solution was diluted with water (50ml) and extracted with ethyl acetate (150ml). The ethyl acetate phase was washed sequentially with water and brine, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to yield the title compound as a white solid (1.4g).

^{1}H-NMR ($CDCl_3$): δ = 7.58 (1H, s), 7.19-7.37 (10H, m), 5.95 (1H, br d), 5.69 (1H, br d), 5.00 (1H, q), 4.50-4.62 (1H, br), 4.20-4.40 (3H, m), 3.90-4.05 (1H, m), 3.75 (1H, t).

It will be appreciated that what will be claimed is as follows:

(i) a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(ii) a process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof;

(iii) a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;

(iv) a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;

(v) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having A2a receptor agonist activity;

(vi) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of an anti-inflammatory agent;

(vii) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of a respiratory disease;

(viii) use as in (vii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema and rhinitis;

(ix) the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of septic shock, male erectile dysfunction, hypertension, stroke, cerebral ischemia, peripheral vascular disease, wound healing or a psychotic disorder;

(x) a method of treatment of a mammal, including a human being, with a A2a receptor agonist including treating said mammal with an effective

amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xi) a method of treatment of a mammal, including a human being, to treat an inflammatory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xii) a method of treatment of a mammal, including a human being, to treat a respiratory disease including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof;

(xiii) a method as in (xii) where the disease is selected from the group consisting of adult respiratory distress syndrome (ARDS), bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema and rhinitis;

(xiv) a method of treatment of a mammal, including a human being, to treat septic shock, male erectile dysfunction, hypertension, stroke, cerebral ischemia, peripheral vascular disease, wound healing or a psychotic disorder including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt, solvate or composition thereof; and

(xv) any novel intermediate disclosed herein.